1: Brain Res Dev Brain Res 1996 Mar 29;92(1):10-7

Related Articles, Books, LinkOut

Ontogeny of NMDA R1 subunit protein expression in five regions of rat brain.

Luo J, Bosy TZ, Wang Y, Yasuda RP, Wolfe BB.

Department of Pharmacology, Georgetown University School of Medicine, Washington, DC 20007, USA.

A polyclonal antiserum to a fusion protein corresponding to a region of the NMDA R1 (NR1) subunit (amino acids 656-811) was produced and affinity purified. A quantitative immunoblotting technique was developed using the fusion protein as a standard. By employing this method, ontogenic studies (day 2-42) of the density of NR1 protein were carried out in several regions of rat brain. The results showed that in all five of the brain regions examined [olfactory bulb (Ob), cortex (Cx), hippocampus (Hp), midbrain (Mb) and cerebellum (Cb)], levels of NR1 protein are low at birth and increase with similar patterns having a sharp rise within the first 3 weeks after birth. Levels increased 2.0 to 4.5-fold from postnatal day 2 to postnatal day 42. Although the general patterns of developmental expression are similar, large differences in the absolute amounts of NR1 protein among the five brain regions were observed. The maximal levels (pmol of fusion protein equivalent/mg +/- S.E.) of NR1 subunit attained during development in the five regions are: Hp 2.0 +/- 0.37 > Cx 1.4 +/- 0.11 > Ob 1.3 +/- 0.2 > Mb 1.0 +/- 0.10 > Cb 0.57 +/- 0.13. The temporal patterns of expression of NR1 protein are similar to results from studies examining the expression of NR1 mRNA. Furthermore, the absolute numbers obtained from our studies are close to those found using [(3)H]MK-801 binding suggesting that many of the NR1 subunits expressed in the brain exist in an active form.

PMID: 8861717 [PubMed - indexed for MEDLINE]

1: J Recept Signal Transduct Res 1995 Jan-Mar;15(1-4):393-411

Immunobiochemical characterization of the NMDA-receptor subunit NR1 in the developing and adult rat brain.

Benke D, Wenzel A, Scheuer L, Fritschy JM, Mohler H.

Institute of Pharmacology, University of Zurich.

To investigate the developmental and regional expression of the NR1-subunit of the NMDA-receptor on the protein level, two polyclonal antisera [NR1(N) and NR1(C)] were raised against fusion proteins derived from the N- and C-terminal domain of the NR1-subunit, respectively. In Western blots of rat brain membranes, both antisera specifically recognized a single protein band with an apparent molecular size of 115 kDa. The regional distribution of the NR1-subunit immunoreactivity was analyzed in the developing and adult rat brain using sections blotted onto nitrocellulose membranes for immunostaining. With the NR1(N)-antiserum, strongest signals were detected in hippocampus, followed by cortex, striatum and thalamus, and weaker staining was observed in tectum, brainstem and cerebellum of adult brain. The NR1(C)-immunoreactivity exhibited a similar distribution, except that the staining in thalamus, tectum, brainstem and cerebellum was faint or virtually absent. The distinct pattern of NR1(N)- and NR1(C)-immunoreactivity arose during postnatal development. At birth, moderate staining with both NR1-subunit antisera was observed throughout the brain increasing strongly in most brain regions until postnatal day 21. In some brain areas, however, the NR1(C)-, in contrast to the NR1(N)-staining, decreased postnatally e.g. in thalamus, tectum and brainstem. The restricted staining intensity of the NR1(C)-antiserum in particular areas of adult and developing brain appears to reflect the emergence of C-terminal splice variants of the NR1-subunit which are not recognized by the NR1(C)-antiserum.

PMID: 8903953 [PubMed - indexed for MEDLINE]

1: Proc Natl Acad Sci U S A 1994 Jan 18;91(2):564-8

Regional, cellular, and ultrastructural distribution of N-methyl-D-aspartate receptor subunit 1 in monkey hippocampus.

Siegel SJ, Brose N, Janssen WG, Gasic GP, Jahn R, Heinemann SF, Morrison JH.

Fishberg Research Center for Neurobiology, Mount Sinai School of Medicine, New York, NY 10029.

The regional, cellular, and subcellular distributions of N-methyl-D-aspartate (NMDA) receptor subunit 1, NMDAR-1, were investigated in monkey hippocampus by using a monoclonal antibody directed against a fusion protein corresponding to aa 660-811 of NMDAR-1. The data indicate that many neurons in each subfield of the hippocampus contain NMDAR-1 protein, although the intensity and distribution of immunoreactivity varied across regions, strata, and cellular compartments. In stratum lucidum of CA3, mossy fiber axons were immunoreactive for NMDAR-1, which may correspond to previously hypothesized presynaptic receptors. NMDAR-1-labeled postsynaptic profiles were present in stratum radiatum of CA3 but were largely absent from stratum lucidum. Such intraneuronal segregation of glutamate receptor subunits or classes may be spatially correlated with afferent systems that exhibit laminar segregation and terminate in different portions of the postsynaptic dendritic tree. For example, in CA3 pyramidal cells, NMDA receptors are postsynaptic in distal apical dendrites (stratum radiatum) where NMDA-dependent long-term potentiation in rats is mediated by associational/commissural afferents, and are absent from proximal apical dendrites (stratum lucidum), where NMDA-independent long-term potentiation is mediated by the mossy fiber input.

PMID: 8290563 [PubMed - indexed for MEDLINE]

1: Nature 1999 Jul 8;400(6740):173-7 Related Articles, Books, OMIM, LinkOut

Comment in:
- Nature. 1999 Jul 8;400(6740):116-7

nature

Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse.

Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandevert C, Walker S, Wogulis M, Yednock T, Games D, Seubert P.

Elan Pharmaceuticals, South San Francisco, California 94080, USA. dschenk@elanpharma.com

Amyloid-beta peptide (Abeta) seems to have a central role in the neuropathology of Alzheimer's disease (AD). Familial forms of the disease have been linked to mutations in the amyloid precursor protein (APP) and the presenilin genes. Disease-linked mutations in these genes result in increased production of the 42-amino-acid form of the peptide (Abeta42), which is the predominant form found in the amyloid plaques of Alzheimer's disease. The PDAPP transgenic mouse, which overexpresses mutant human APP (in which the amino acid at position 717 is phenylalanine instead of the normal valine), progressively develops many of the neuropathological hallmarks of Alzheimer's disease in an age- and brain-region-dependent manner. In the present study, transgenic animals were immunized with Abeta42, either before the onset of AD-type neuropathologies (at 6 weeks of age) or at an older age (11 months), when amyloid-beta deposition and several of the subsequent neuropathological changes were well established. We report that immunization of the young animals essentially prevented the development of beta-amyloid-plaque formation, neuritic dystrophy and astrogliosis. Treatment of the older animals also markedly reduced the extent and progression of these AD-like neuropathologies. Our results raise the possibility that immunization with amyloid-beta may be effective in preventing and treating Alzheimer's disease.

PMID: 10408445 [PubMed - indexed for MEDLINE]

1: Nature 2000 Dec 21-28;408(6815):982-5 Related Articles, Books, OMIM, LinkOut

Comment in:
- Nature. 2000 Dec 21-28;408(6815):915-6

nature

A beta peptide vaccination prevents memory loss in an animal model of Alzheimer's disease.

Morgan D, Diamond DM, Gottschall PE, Ugen KE, Dickey C, Hardy J, Duff K, Jantzen P, DiCarlo G, Wilcock D, Connor K, Hatcher J, Hope C, Gordon M, Arendash GW.

Department of Pharmacology, University of South Florida, Tampa 33612, USA. dmorgan@hsc.usf.edu

Vaccinations with amyloid-beta peptide (A beta) can dramatically reduce amyloid deposition in a transgenic mouse model of Alzheimer's disease. To determine if the vaccinations had deleterious or beneficial functional consequences, we tested eight months of A beta vaccination in a different transgenic model for Alzheimer's disease in which mice develop learning deficits as amyloid accumulates. Here we show that vaccination with A beta protects transgenic mice from the learning and age-related memory deficits that normally occur in this mouse model for Alzheimer's disease. During testing for potential deleterious effects of the vaccine, all mice performed superbly on the radial-arm water-maze test of working memory. Later, at an age when untreated transgenic mice show memory deficits, the A beta-vaccinated transgenic mice showed cognitive performance superior to that of the control transgenic mice and, ultimately, performed as well as nontransgenic mice. The A beta-vaccinated mice also had a partial reduction in amyloid burden at the end of the study. This therapeutic approach may thus prevent and, possibly, treat Alzheimer's dementia.

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1: Nature 2000 Dec 21-28;408(6815):979-82

Related Articles, Books, OMIM, LinkOut

Comment in:

- Nature. 2000 Dec 21-28;408(6815):915-6

nature

A beta peptide immunization reduces behavioural impairment and plaques in a model of Alzheimer's disease.

Janus C, Pearson J, McLaurin J, Mathews PM, Jiang Y, Schmidt SD, Chishti MA, Horne P, Heslin D, French J, Mount HT, Nixon RA, Mercken M, Bergeron C, Fraser PE, St George-Hyslop P, Westaway D.

Centre for Research in Neurodegenerative Diseases, Department of Medicine, University of Toronto, Ontario, Canada.

Much evidence indicates that abnormal processing and extracellular deposition of amyloid-beta peptide (A beta), a proteolytic derivative of the beta-amyloid precursor protein (betaAPP), is central to the pathogenesis of Alzheimer's disease (reviewed in ref. 1). In the PDAPP transgenic mouse model of Alzheimer's disease, immunization with A beta causes a marked reduction in burden of the brain amyloid. Evidence that A beta immunization also reduces cognitive dysfunction in murine models of Alzheimer's disease would support the hypothesis that abnormal A beta processing is essential to the pathogenesis of Alzheimer's disease, and would encourage the development of other strategies directed at the 'amyloid cascade'. Here we show that A beta immunization reduces both deposition of cerebral fibrillar A beta and cognitive dysfunction in the TgCRND8 murine model of Alzheimer's disease without, however, altering total levels of A beta in the brain. This implies that either a approximately 50% reduction in dense-cored A beta plaques is sufficient to affect cognition, or that vaccination may modulate the activity/abundance of a small subpopulation of especially toxic A beta species.

PMID: 11140685 [PubMed - indexed for MEDLINE]